EXHIBIT 10

Excerpts from the Reply Expert Report of Jay W. Heinecke, M.D. Dated June 7, 2019

UNITED STATES DISTRICT COURT
DISTRICT OF NEVADA

AMARIN PHARMA, INC. and AMARIN PHARMACEUTICALS IRELAND LIMITED Plaintiffs, v. HIKMA PHARMACEUTICALS USA INC. and HIKMA PHARMACEUTICALS INTERNATIONAL LIMITED, Defendants.	Case No. 2:16-cv-02525-MMD-NJK (CONSOLIDATED) Judge: Miranda M. Du **CONFIDENTIAL**

REPLY EXPERT REPORT OF JAY W. HEINECKE, M.D. ON INVALIDITY OF THE ASSERTED CLAIMS OF THE PATENTS-IN-SUIT

DHA or an EPA-DHA mixture, that would not have made purified EPA—which was commercially available as Epadel and had been studied in multiple clinical trials—any less obvious. *Infra*, Part VI.A.

20. Dr. Toth also opines that a POSA as of March 2008 would not have found it obvious to use a daily dosage of 4 g or about 4 g, as required by all asserted claims. I disagree. As discussed below, it remains my opinion that a POSA as of March 2008 would have found it obvious to use (or at least try) a daily dosage of 4 g, which was disclosed as an effective, triglyceride-lowering dosage in Mori 2000 for purified EPA, and in the Lovaza® PDR for treating patients with baseline triglyceride levels of at least 500 mg/dL. (Mori 2000 at 1085-88; Lovaza® PDR at 2700.) Even if a POSA had also found it obvious to try other dosages, that would not have made a daily dosage of 4 g any less obvious. *Infra*, Part VI.B.

21. Dr. Toth further disputes that the purity and clinical effects required by some asserted claims (for example, effects on LDL-C or Apo B levels) would have been obvious to a POSA as of March 2008. I disagree. These elements, which only certain asserted claims require, were expressly taught in the prior-art references set forth in my opening report, which would have provided a POSA with a reasonable expectation of success in achieving each of the claimed limitations and the claimed inventions as a whole. *Infra*, Part VI.C.

22. Dr. Toth relies on and incorporates his opinions on alleged objective indicia of nonobviousness set forth in his opening report. (*E.g.*, Toth Rebuttal Rept. ¶¶ 367, 545.) I addressed Dr. Toth's opinions on alleged objective indicia of nonobviousness in my rebuttal report, which I fully incorporate here. (Heinecke Rebuttal Rept. ¶¶ 58-196.)

23. I may testify at trial about the opinions discussed in this expert report and any supplemental reports or declarations that I may prepare for this case, as well as present a tutorial

on background scientific concepts to better explain the context of the technology at issue. I may also testify at trial regarding matters addressed by other witnesses, and prepare demonstratives to better help me explain my opinions. The bases for my opinions include the documents and prior art cited in this report, my education, and my years of experience and research. I reserve the right to amend or supplement my report if additional facts or information become available.

IV. LEVEL OF ORDINARY SKILL

24. In my opening report, I provided my opinion regarding the level of ordinary skill in the art to which the asserted patents pertain, which I applied in evaluating whether the asserted claims would have been obvious to a POSA as of March 2008. (Heinecke Opening Rept. ¶¶ 37-40.) Dr. Toth states that he disagrees with my proposed definition, but only because it "appears to provide that a person of ordinary skill in the art could have no medical degree and no clinical experience treating hypertriglyceridemia." (Toth Rebuttal Rept. ¶ 15.)

25. To be clear, under my definition, a POSA would have had a high level of skill relevant to the asserted patents. As explained in my opening report, a POSA would "have had at least a medical degree or an advanced degree in the field of lipid biochemistry," as well as "several years of experience in the development and/or clinical use of fatty acids to treat blood lipid disorders, including fish oil based fatty acids, i.e., EPA and DHA, and their dosage forms," and would have had "access to a team including one or more of a medical doctor, an analytical chemist familiar with lipids and fish oils, or a person working with lipids and fish oils, a lipid biochemist, a pharmaceutical chemist or a person working in a comparable field with an advanced degree (such as a Ph.D. or M.D.)," as appropriate. (Heinecke Opening Rept. ¶ 37.) I only noted that a POSA "could have a lower level of formal education if such person has a higher degree of experience"—e.g., in treating patients with, or researching therapies for the treatment of, lipid disorders including hypertriglyceridemia. (*Id.*) Thus, to the extent that Dr.

Toth suggests that my definition of a POSA would include a person or team that is underqualified to treat patients or assess treatments for hypertriglyceridemia, I disagree.

26. As I explained in my rebuttal report, I disagree with Dr. Toth's proposed definition of a POSA for a similar reason: it appears to include a nurse practitioner or physician's assistant, whereas the asserted patents are directed to a person with a higher level of ordinary skill than a nurse practitioner or physician's assistant. (Heinecke Rebuttal Rept. ¶ 22.) It remains my opinion that, as compared to Dr. Toth's definition of a POSA, my definition better reflects the level of ordinary skill to which the asserted patents are directed.

27. Nevertheless, as I noted in my rebuttal report, any difference between my definition of a POSA and Dr. Toth's is not material to my opinions in this case. (*Id.* ¶ 23.) My opinions regarding the obviousness of the asserted claims are the same regardless of whose definition is adopted. My background and qualifications meet both definitions of a POSA today, and did so as of the earliest priority date in March 2008.

V. PROSECUTION HISTORY

28. With respect to the prosecution history of the asserted patents, Dr. Toth agrees with my focus on the prosecution of U.S. Patent No. 8,293,727 (the "'727 patent"), which I understand is a previous patent that is related to the asserted patents. (Toth Rebuttal Rept. ¶ 287; Heinecke Opening Rept. ¶ 246.) Dr. Toth disagrees, however, with my opinion that the patent examiner, in allowing the '727 patent and the asserted patents to issue, relied on "declarations from Dr. Philip Lavin stating that there were no subjects in the Hayashi reference that had triglyceride levels of at least 500 mg/dl." (Toth Rebuttal Rept. ¶ 291.) Instead, according to Dr. Toth, the examiner relied only "on objective indicia of nonobviousness—in particular, a showing that the applicants demonstrated unexpected results (an unexpected reduction in apoB), and satisfied a long-felt unmet medical need, in that their method of treatment lowered triglycerides

vi. There was no relevant skepticism about using purified EPA to avoid increasing LDL-C levels.

68. Sixth, I disagree with Dr. Toth's opinion that there was relevant skepticism as to whether purified EPA would reduce triglycerides without increasing LDL-C levels. (Toth Rebuttal Rept. ¶¶ 55-57.) I addressed the same purported evidence of skepticism in my rebuttal report, which I incorporate here. (Heinecke Rebuttal Rept. ¶¶ 181-83.) Again, Dr. Toth cites comments from "an expert panel meeting" hosted by Amarin. (Toth Rebuttal Rept. ¶ 56.) But Dr. Toth cites no evidence that the "experts" he relies on to show skepticism were aware of prior-art studies such as Mori 2000 and Kurabayashi, which showed that purified EPA reduced triglyceride levels without increasing LDL-C levels. Indeed, in reporting the results of the MARINE study, Amarin itself cited those prior-art studies as "suggest[ing] that highly purified eicosapentaenoic acid lowered triglyceride (TG) levels without increasing low-density lipoprotein (LDL) cholesterol levels." (Bays[11] at 682, 688, 690.)

69. Dr. Toth also relies on supposed skepticism about whether mixtures of EPA and DHA would reduce triglycerides without increasing LDL-C levels. (Toth Rebuttal Rept. ¶ 57.) But again, a POSA would have understood from the prior art that purified EPA was different than a mixture of EPA and DHA. Nothing in Dr. Toth's report shows otherwise.

70. Dr. Toth's view that a POSA would have expected purified EPA to have different effects on LDL-C levels depending on whether a patient's baseline triglyceride levels were at least 500 mg/dL contradicts the opinion in his opening report that "there is a strong basis to conclude that such individuals will experience the cardiovascular benefit observed in REDUCE-

[11] Bays et. al, *Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Patients With Very High Triglyceride Levels (from the multi-center, placebo-controlled, randomized, double-blind, 12-week study with an open-label Extension [MARINE] Trial),* 108 Am. J. Cardiol. 682 (2011).

IT when their TG levels are 500 mg/dl or greater, even though subjects in the REDUCE-IT trial had TG levels ranging from 135 mg/dl to 499 mg/dl at enrollment." (Toth Opening Rept. ¶ 173.) Dr. Toth cannot have it both ways. If there is "a strong basis to conclude" that the REDUCE-IT results apply to patients with triglyceride levels of at least 500 mg/dL, then a POSA as of March 2008 would have had an equally strong basis to reasonably expect that the results of prior-art studies on purified EPA in patients with lower triglyceride levels would also apply to patients with triglyceride levels of at least 500 mg/dL.

71. I also note that the asserted patents contain no data or results whatsoever, let alone data on LDL-C levels for patients with triglyceride levels of at least 500 mg/dL. The patents' shared specification simply asserts, without any supporting data, that the claimed methods may result in "no increase in LDL-C levels compared to baseline," among other effects. (*E.g.*, 728 pat. 4:10; *see also, e.g.*, *id*. at 5:37-46.) The only example in the specification—a study protocol that appears to be based on MARINE—makes clear that the study had not yet occurred, and the results had not yet been obtained. (*Id.* at 13:24-16:50.) The specification repeatedly states that patients "*will be* randomized," "[t]he study *will be* a . . . Phase 3, multi-center study," "[t]he screening visit (Visit 1) *will occur*," "eligible patients *will* enter a 12-week, randomized, double-blind treatment period," and "[t]he primary efficacy variable *will be* the percent change in fasting TG levels from baseline to Week 12," among other examples. (*Id*. (emphasis added).) Indeed, the entire description of the proposed study is in the future tense. (*Id*.) Thus, if Dr. Toth were correct that a POSA would not have expected purified EPA to reduce triglycerides without increasing LDL-C levels in patients with baseline triglycerides of at least 500 mg/dL based on the prior art (an assumption I disagree with), then a POSA would not have believed that the inventors of the asserted patents had achieved that result based on the specification either.

72. For at least these reasons, I disagree with Dr. Toth's premise that a POSA would have assumed that triglyceride-lowering therapy with purified EPA would have a different effect on LDL-C levels in patients with baseline triglyceride levels of at least 500 mg/dL than in patients with lower baseline triglyceride levels.

b. Dr. Toth incorrectly criticizes each prior-art reference individually for not being sufficiently "predictive," instead of considering their combined teachings in forming a reasonable expectation of success.

73. Once it becomes clear that there was no expectation that purified EPA would have a different effect on LDL-C levels in patients with triglyceride levels of at least 500 mg/dL than in patients with lower levels, it becomes equally clear that the prior-art references that I relied on in combination with the Lovaza® PDR would have motivated a POSA as of March 2008 to substitute purified EPA for the EPA + DHA mixture disclosed in the Lovaza® PDR with a reasonable expectation of success, for all of the reasons explained in my opening report. (*See, e.g.*, Heinecke Opening Rept. ¶¶ 296-06, 560-70, 623-33.)

74. In opining otherwise, Dr. Toth criticizes the studies I cited individually to conclude that they were "not predictive of the LDL-C effects in persons with TG levels of at least 500 mg/dl." (Toth Rebuttal Rept. ¶¶ 319-45.) I understand, however, that obviousness does not require absolute predictability. I understand that only a reasonable expectation that the beneficial result will be achieved is necessary. Moreover, I understand that a finding of obviousness cannot be avoided by attacking references individually where the finding is based upon the teachings of a combination of references. In my opinion, Dr. Toth's analysis does not comport with these principles. In any event, I disagree with his criticisms of the prior-art references that I relied on in combination with the Lovaza® PDR.

179. Nozaki only studied a lower-purity 90% EPA product, at a lower daily dosage of 2.7 g, in patients with lower baseline triglyceride levels of 165 ± 25 mg/dL. (Nozaki at 256-58; Toth Rebuttal Rept. ¶ 148.) The fact that Nozaki observed a 16% reduction in triglyceride levels under those conditions would not have changed a POSA's reasonable expectation that at least 96% pure EPA, administered at a daily dosage of 4 g in a patient with baseline triglyceride levels of at least 500 mg/dL, would achieve the claimed reduction of about 25%.

180. Park disclosed a study that was limited to patients with "TG concentrations less than 200 mg/dl." (Park at 455.) In fact, as Dr. Toth acknowledges, baseline triglyceride levels in the EPA group were only 75 mg/dL. (*Id*. at 457, Table 2; Toth Rebuttal Rept. ¶ 374.) Under Dr. Toth's own classification system, those are not even borderline-high triglyceride levels (150-199 mg/dL). (Toth Rebuttal Rept. ¶ 28.) The fact that EPA produced only a 9% reduction in triglyceride levels that were already low would not have changed a POSA's reasonable expectation that purified EPA, when administered to a patient with baseline triglyceride levels of at least 500 mg/dL, would achieve the claimed reduction of about 25%.

181. The study reported in Saito administered a daily dosage of either 1.8 g or 2.7 g EPA—not about 4 g. (Saito at 2048.) Dr. Toth cites the average reduction in triglyceride levels of 13.3%, but ignores the substantial difference in results between the two dosage groups. (Toth Rebuttal Rept. ¶ 374 (citing Saito at 2054).) In particular, triglyceride levels decreased by 21.9% in patients taking 2.7 g/day, but only by 7.6% in patients taking 1.8 g/day. (Saito at 2054.) Thus, a POSA would have reasonably expected that a higher daily dosage than 2.7 g (e.g., 4 g) would provide an even greater reduction in triglyceride levels (e.g., 25%).

182. Satoh similarly reported a study that administered only a daily dosage of 1.8 g purified EPA, and only in obese type-2 diabetic patients. (Satoh at 144.) The 19% reduction in

triglyceride levels observed in Satoh at that dosage and in that patient population would not have changed a POSA's reasonable expectation that purified EPA, when administered at a daily dosage of about 4 g, would achieve the claimed reduction of about 25%.

183. I also note that the asserted patents contain no data or results whatsoever, let alone data on the reduction in triglyceride levels achieved with a daily dosage of 4 g in patients with triglyceride levels of at least 500 mg/dL. The patents' shared specification simply asserts, without any supporting data, that the claimed methods may result in "a reduction in triglyceride level" of up to "at least about 75%" compared to baseline. (*E.g.*, '728 pat. 5:11-20.) The only example in the specification—a study protocol that appears to be based on MARINE—makes clear that the study had not yet occurred, and the results had not yet been obtained. (*Id.* at 13:24-16:50.) Indeed, the example states that "[t]he primary efficacy variable *will be* the percent change in fasting TG levels from baseline to Week 12," thus confirming that any reduction in triglyceride levels had not yet been evaluated. (*Id*. at 16:41-42 (emphasis added).) Thus, if Dr. Toth were correct that a POSA would not have expected purified EPA to reduce triglyceride levels by at least 25% based on the prior art (an assumption I disagree with), then a POSA would not have believed that the inventors of the asserted patents had achieved that result based on the specification either.

184. In sum, none of the evidence cited by Dr. Toth changes my opinion that a POSA would have reasonably expected that administering a daily dosage of about 4 g purified EPA to a patient with baseline triglyceride levels of at least 500 mg/dL for 12 weeks or more would reduce the patient's triglyceride levels by at least about 25%, which includes the lower claimed thresholds of at least about 10%, 15%, 20%, and by a statistically significant amount. Thus, it remains my opinion that the asserted claims that require those specific minimum reductions in

triglyceride levels would have been obvious, as a whole, to a POSA as of March 2008 in view of the combinations of prior-art references that I set forth in my opening report.

b. A POSA would have reasonably expected the reduction or lack of increase in LDL-C levels required by some claims.

185. A number of asserted claims require reducing or not increasing the patient's LDL-C levels. Specifically:

- All asserted claims of the '728, '677, '652, and '446 patents reducing triglyceride levels "without substantially increasing LDL-C." ('728 pat. claims 1, 6, 13, 16, 17, and 18; '677 pat. claims 1, 7, and 8; '652 pat. claims 1, 7, 8, 10, 16, and 17; '446 pat. claims 1 and 6.)
- Claim 4 of the '715 patent requires "substantially no increase in LDL-C levels."
- Claims 13-15 of the '715 patent require reducing triglyceride levels "without effecting a statistically significant increase in LDL-C."
- Claims 7 and 17 of the '560 patent require reducing triglyceride levels "without increasing LDL-C."
- Claims 4 and 14 of the '560 patent require reducing triglyceride levels "without increasing LDL-C by more than 5%."
- Claim 18 of the '335 patent requires "a reduction in fasting LDL-C."

It remains my opinion that each of these asserted claims, as a whole, would have been obvious to a POSA as of March 2008 in view of the combinations of prior-art references that I set forth in my opening report.

186. As discussed in the sections above, Dr. Toth disputes that a POSA would have reasonably expected that purified EPA would reduce triglyceride levels without raising LDL-C levels in a patient with baseline triglyceride levels of at least 500 mg/dL. (*E.g.*, Toth Rebuttal Rept. ¶¶ 41-57, 317-45.) For all of the reasons discussed above, which I incorporate here by reference, I disagree with Dr. Toth. In my opinion, a POSA would have reasonably expected purified EPA to reduce triglyceride levels without raising LDL-C levels in a patient with baseline

triglyceride levels of at least 500 mg/dL, at least in view of the Lovaza® PDR, Mori 2000, and optionally Hayashi and/or Kurabayashi. (*Supra* ¶¶ 47-72.) Thus, the limitations in some asserted claims that require reducing triglyceride levels without increasing LDL-C levels do not change my opinion that those claims would have been obvious to a POSA as of March 2008 in view of the combinations of prior-art references that I set forth in my opening report.

187. As for claim 18 of the '335 patent, which requires "a reduction in fasting LDL-C," I explained in my opening report that at least Hayashi, as well as a number of background prior-art references, reported that purified EPA reduces LDL-C levels. (Heinecke Opening Rept. ¶ 240 (citing Hayashi at 26 (reporting 7% reduction in LDL-C levels); Grimsgaard 1997 at 653 (reporting 8% reduction in LDL-C levels); Nozaki at 257-58 (reporting "significant" reduction in LDL-C levels); Satoh at 144 (reporting "significant reductions" in LDL-C levels)); *see also id*. ¶¶ 98, 114, 82, 85, 203 (discussing reductions in LDL-C levels reported in Hayashi, Grimsgaard 1997, Nozaki, and Satoh, respectively).)

188. Dr. Toth opines that "this limitation would not have been obvious for the same reasons that it would not have been obvious that the claimed method would avoid a substantial increase in LDL-C in subjects with very high triglycerides," and he incorporates his prior "discussion concerning the expected effect of high purity EPA on LDL-C." (Toth Rebuttal Rept. ¶ 582 (citing *id*. ¶¶ 314-45).) Likewise, I incorporate my discussion above responding to Dr. Toth's opinions, with which I disagree. (*Supra* ¶¶ 47-72.)

189. I also note that the asserted patents contain no data or results whatsoever, let alone data on any reduction in LDL-C levels in patients with triglyceride levels of at least 500 mg/dL. The patents' shared specification simply asserts, without any supporting data, that the claimed methods may result in "a reduction in LDL-C levels" of up to "at least about 75%" compared to

baseline. (*E.g.*, '728 pat. 5:40-46.) The only example in the specification—a study protocol that appears to be based on MARINE—makes clear that the study had not yet occurred, and the results had not yet been obtained. (*Id.* at 13:24-16:50.) Thus, if Dr. Toth were correct that a POSA would not have expected purified EPA to reduce fasting LDL-C levels (an assumption I disagree with), then a POSA would not have believed that the inventors of the asserted patents had achieved that result based on the specification either.

190. Thus, I stand by my opinion that claim 18 of the '335 patent would have been obvious to a POSA as of March 2008 for the reasons discussed in my opening report. (*E.g.*, Heinecke Opening Rept. ¶¶ 551-56.)

c. A POSA would have reasonably expected the reduction or lack of increase in Apo B levels required by some claims.

191. A number of asserted claims require reducing or not increasing the patient's Apo B levels. Specifically:

- Claims 1, 4, 8, 11, and 18 of the '715 patent, claim 8 of the '677 patent, claim 8 of the '652 patent, and claim 6 of the '446 patent require administering purified EPA "to effect a reduction" in Apo B levels.
- Claims 13-15 of the '715 patent require reducing triglyceride levels "without effecting a statistically significant increase" in Apo B levels.
- Claim 14 of the '715 patent further requires administering purified EPA "to effect a statistically significant reduction" in Apo B levels.
- Claims 14 and 18 of the '335 patent, claim 17 of the '652 patent, claim 5 of the '929 patent, and claim 4 of the '698 patent require that the claimed methods be "effective to reduce" Apo B levels.
- Claim 5 of the '560 patent requires that the claimed method "effects a reduction" in Apo B levels.

It remains my opinion that each of these asserted claims, as a whole, would have been obvious to a POSA as of March 2008 in view of the combinations of prior-art references that I set forth in my opening report.

192. As I explained, a POSA as of March 2008 would have reasonably expected purified EPA to reduce Apo B levels in view of at least Mori 2000, Hayashi, and Kurabayashi—including based on the statistically significant reduction in Apo B levels reported in Kurabayashi. (*E.g.*, Heinecke Opening Rept. ¶¶ 360-61.) I also cited background prior-art references that would have confirmed that reasonable expectation, including Nozaki and Grimsgaard 1997. (*E.g.*, *id*. ¶¶ 87-88, 90 (Nozaki), 113 (Grimsgaard 1997), 240 (both).) I disagree with Dr. Toth's reasons for disputing my opinions. (*E.g.*, Toth Rebuttal Rept. ¶¶ 419-33.)

193. As an initial matter, Dr. Toth states that none of these prior-art references "studied the lipid effects of high purity EPA in a population with very high triglyceride levels," and opines that a POSA "would not have looked to these references in forming an expectation about the effect of high purity EPA on apoB in persons with very high triglycerides." (*Id*. ¶ 420; *see also, e.g.*, *id*. ¶¶ 147, 158-59, 432-33.) Dr. Toth opines that a POSA "would instead have looked to the experience with LOVAZA®, which was the only FDA-approved omega-3 fatty acid for lowering triglycerides in persons with very high triglycerides." (*Id*.; *see also id*. ¶¶ 421-23.) For all of the reasons I discussed above, I disagree. (*Supra* ¶¶ 48-52, 91-94.)

194. Again, at least Hayashi included some patients with baseline triglyceride levels of at least 500 mg/dL, and in any event, a POSA as of March 2008 would have formed a reasonable expectation about the effects of purified EPA in patients with baseline triglyceride levels of at least 500 mg/dL even from references that did not specifically study patients with those levels. (*Id*.) Moreover, a POSA would have focused on studies on purified EPA—not studies on Lovaza®, which a POSA would have understood to have different effects on lipids than purified EPA because it contained a substantial proportion of DHA. (*Id*.) Thus, it remains my opinion that a POSA would have relied on Mori 2000, Hayashi, and Kurabayashi, as well as Nozaki and

Grimsgaard 1997 as relevant background references, in forming reasonable expectations about the effects of purified EPA on Apo B levels.

195. ***Mori 2000.*** Dr. Toth denies that a POSA as of 2008 would have understood Mori 2000 to report Apo B levels in patients taking purified EPA. (Toth Rebuttal Rept. ¶ 425.) As I explained in my opening report, however, a POSA would have calculated approximate Apo B levels from the results in Mori 2000 by subtracting the reported HDL-C levels from total cholesterol levels to obtain non-HDL-C levels, which a POSA would have understood to be closely correlated to Apo B levels. (Heinecke Opening Rept. ¶ 360.) Indeed, based on the prior-art ATP-III guidelines, Amarin admits that "[b]ecause both non-HDL-C and Apo-B are essentially measuring the same value—presence of atherogenic lipoproteins in the blood stream—non-HDL-C was understood to be correlated with total Apo-B and to 'represent[] an acceptable surrogate marker for total [Apo-B] in routine clinical practice.'" (Preliminary Validity Contentions at 31 (quoting ATP-III at 3170).)

196. Dr. Toth cites instances in which non-HDL-C levels might not absolutely predict Apo B levels. (Toth Rebuttal Rept. ¶¶ 429-30.) Again, however, I understand that obviousness does not require absolute predictability. I understand that only a reasonable expectation that the beneficial result will be achieved is necessary. Here, Dr. Toth admits that "non-HDL-C correlates to a considerable degree with apoB," and that "non-HDL-C was understood to represent an acceptable surrogate marker for total apoB in routine clinical practice." (*Id*. ¶¶ 429, 431 (quotation and alterations omitted).) Thus, even if Apo B levels were not absolutely predictable, non-HDL-C levels would have been sufficient for a POSA to form a reasonable expectation about the likely Apo B levels in the Mori 2000 study.

197. Dr. Toth notes that the reduction in non-HDL-C levels reported in Mori 2000 (and thus the expected approximate reduction in Apo B levels) was 0.58% from baseline. (*Id*. ¶¶ 426-27.) Dr. Toth states that there was no reduction relative to placebo, and opines that the reduction from baseline was "so slight as to be effectively neutral." (*Id*.) None of the asserted claims, however, requires any comparison to a patient taking a placebo. While some claims state that lipid effects are "compared to" a second patient who is not taking purified EPA, I understand that the Court construed this language as "not a claim limitation," and that "the claimed effect can be compared to 'the *expectation* if the subject did not receive purified ethyl-EPA.'" (August 10, 2018 Claim Construction Order, D.I. 135 at 12; Heinecke Opening Rept. ¶ 32(e).) Nor do any of the asserted claims require any particular degree of reduction in Apo B levels—they cover *any* reduction in Apo B levels, no matter how "slight." (Toth Rebuttal Rept. ¶ 427.) Moreover, some of the asserted claims with limitations regarding Apo B merely require the lack of any *increase* in Apo B levels. ('715 pat. claims 13, 15, and 18.) Thus, it remains my opinion that Mori 2000 disclosed a reduction or lack of increase in Apo B levels within the scope of the asserted claims.

198. ***Hayashi.*** Dr. Toth denies that Hayashi showed a reduction in LDL-C levels for patients taking purified EPA—despite reporting a 7% reduction—because the change was neither statistically significant compared to baseline nor compared to placebo. (Toth Rebuttal Rept. ¶ 432; Hayashi at 26, Table I.) Many of the asserted claims with limitations regarding Apo B, however, do not require a statistically significant reduction (and for those claims that do, as discussed below, Kurabayashi disclosed such a reduction). (*Supra* ¶ 191.) And again, none of the asserted claims as construed requires any actual comparison to a patient taking a placebo.

Rather, the asserted claims cover any degree of reduction (and in some cases, merely a lack of any increase) in Apo B levels from baseline. (*Id.*)

199. ***Kurabayashi.*** Dr. Toth denies that Kurabayashi showed a reduction in LDL-C levels for patients taking purified EPA—despite showing a statistically significant reduction of 6.9%—because all patients in the study were also taking estriol. (Toth Rebuttal Rept. ¶ 433; Kurabayashi at 523, 525, Table 3.) None of the asserted claims, however, excludes the use of estriol. All asserted claims recite methods of treatment "comprising" certain steps, and I understand that this transitional phrase means that other elements may be added and still form a construct within the scope of the claim. Thus, all asserted claims cover the treatment of patients with EPA and estriol. Kurabayashi's Apo B results observed in patients taking EPA and estriol are relevant to the asserted claims for this reason alone.

200. In any event, Dr. Toth cites no reason to believe that estriol significantly affected Apo B levels. In patients taking estriol alone, Apo B levels decreased by only 1.5%, which was not statistically significant. (Kurabayashi at 525, Table 3.) Only the patients taking purified EPA experienced a statistically significant reduction in Apo B levels (i.e., by 6.9%). (*Id.*)

201. Dr. Toth notes that the difference between the EPA group and the estriol-only control group was not itself statistically significant. (Toth Rebuttal Rept. ¶ 433.) Again, however, none of the asserted claims as construed requires an actual comparison to a second patient in a control group. (*Supra* ¶ 197.) At most, some asserted claims require a statistically significant reduction in Apo B levels, which is exactly what Kurabayashi reported for patients taking purified EPA. (Kurabayashi at 523, 525, Table 3.)

202. ***Nozaki.*** Dr. Toth acknowledges that I also relied on Nozaki as relevant background art reporting "that EPA treatment reduced triglycerides, LDL-C, and apoB." (Toth

Rebuttal Rept. ¶ 146; *see also* Heinecke Opening Rept. ¶¶ 87-88, 90, 240.) Indeed, Nozaki reported that "apolipoprotein (apo) B100 levels were significantly reduced ($p < 0.05$)" by EPA. (Nozaki at 257; *see also id*. at 258, Table III (reporting statistically significant reduction in Apo B levels from 142.2 ± 27.9 mg/dL at baseline to 122.5 ± 27.9 mg/dL "after EPA administration").) Dr. Toth's only response is that "EPA was not administered to the very-high TG patient population"—i.e., patients with triglyceride levels of at least 500 mg/dL. (Toth Rebuttal Rept. ¶ 147.) As explained above, however, that would not have prevented a POSA from forming reasonable expectations about the likely effects of EPA on Apo B levels in such patients.

203. ***Grimsgaard 1997.*** Dr. Toth also acknowledges that "Grimsgaard 1997 reported that EPA showed a statistically significant decrease in apoB compared to baseline." (Toth Rebuttal Rept. ¶ 159; *see also* Heinecke Opening Rept. ¶¶ 113, 240; Grimsgaard 1997 at 653, Table 4 (reporting statistically significant 3% reduction in Apo B levels ($p < 0.05$).) Dr. Toth's only response is that "statistical significance was not reached when EPA was compared to placebo," rather than to baseline levels. (Toth Rebuttal Rept. ¶ 159.) Again, however, none of the asserted claims as construed requires any actual comparison to a patient taking a placebo. Rather, the asserted claims cover any degree of reduction (and in some cases, merely a lack of any increase) in Apo B levels from baseline. (*Supra* ¶ 197.)

204. I also note that the asserted patents contain no data or results whatsoever, let alone data on any reduction in Apo B levels in patients with triglyceride levels of at least 500 mg/dL. The patents' shared specification simply asserts, without any supporting data, that the claimed methods may result in "a decrease in Apo B levels" of up to "at least about 75%" compared to baseline. (*E.g.*, '728 pat. 5:47-52.) The only example in the specification—a study protocol that

appears to be based on MARINE—makes clear that the study had not yet occurred, and the results had not yet been obtained. (*Id.* at 13:24-16:50.) Thus, if Dr. Toth were correct that a POSA would not have expected purified EPA to reduce Apo B levels (an assumption I disagree with), then a POSA would not have believed that the inventors of the asserted patents had achieved that result based on the specification either.

205. In sum, Dr. Toth's rebuttal report does not change my opinion that a POSA would have reasonably expected that administering a daily dosage of about 4 g purified EPA to a patient with baseline triglyceride levels of at least 500 mg/dL for 12 weeks or more would reduce the patient's Apo B levels—including by a statistically significant amount. Thus, it remains my opinion that the asserted claims that require a reduction (or lack of increase) in Apo B levels would have been obvious, as a whole, to a POSA as of March 2008 in view of the combinations of prior-art references that I set forth in my opening report.

d. A POSA would have reasonably expected the reduction in non-HDL-C levels required by claim 8 of the '715 patent.

206. Asserted claim 8 of the '715 patent requires "a reduction in non-HDL C of at least about 5%." It remains my opinion that this claim as a whole would have been obvious to a POSA as of March 2008 in view of the combination of prior-art references that I set forth in my opening report. (Heinecke Opening Rept. ¶¶ 367-70.) In particular, as I explained, a POSA would have understood that Hayashi disclosed a 13% reduction in non-HDL-C levels based on the reported total cholesterol and HDL-C levels. (*Id.* ¶ 369; Hayashi at 26, Table I.)

207. Dr. Toth does not dispute that Hayashi disclosed a 13% reduction in non-HDL-C levels. Nor does he dispute that a POSA would have reasonably expected "a reduction in non-HDL C of at least about 5%," as required by claim 8 of the '715 patent, in view of Hayashi. In opining that claim 8 of the '715 patent would not have been obvious, Dr. Toth simply relies on

the same arguments I address in the sections above regarding other limitations of the claim. (Toth Rebuttal Rept. ¶ 441; *supra* ¶¶ 43-102, 110-184, 191-205.) Thus, for the same reasons discussed above and in my opening report, it remains my opinion that asserted claim 8 of the '715 patent would have been obvious, as a whole, to a POSA as of March 2008 in view of the combination of prior-art references that I set forth in my opening report.

3. The claimed patient limitations would have been obvious.

208. Some asserted claims include additional limitations on the patient being treated. There are three categories of such additional patient limitations.

209. First, asserted claims 1, 6, 13, and 16-18 of the '728 patent; and claims 1, 4, 8, 11, 13, 14, 15, and 18 of the '715 patent require that the patient being treated "does not receive concurrent lipid altering therapy" or "is not on concomitant statin therapy."

210. Second, there are three asserted claims that require the patient being treated to have certain baseline levels of various types of cholesterol:

- Asserted claim 6 of the '728 patent (by its dependence from claim 4 of the '728 patent) requires that the patient being treated have "a baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl, a baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or HDL-C of about 10 mg/dl to about 80 mg/dl."
- Asserted claim 18 of the '335 patent (by its dependence from claim 17 of the '335 patent) similarly requires that the patient being treated have "a baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl; a baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl; a baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl; and a baseline fasting HDL-C of about 10 to about 80 mg/dl."
- Asserted claim 4 of the '698 patent (by its dependence from claim 2 of the '698 patent) requires that the patient have "a fasting baseline LDL-C from about 50 mg/dl to about 300 mg/dl."

211. Third, asserted claims 15 and 17 of the '728 patent; and claims 11, 15, and 18 of the '715 patent require that the patient being treated consumes a "Western diet."

212. Although Dr. Toth opines that these claims would not have been obvious, he does not rely on their additional patient limitations. Instead, he simply repeats or incorporates the same arguments regarding other claim elements that I address in previous sections of this report. Thus, for the same reasons discussed above and in my opening report, it remains my opinion that each of these claims as a whole would have been obvious to a POSA as of March 2008 in view of the combinations of prior-art references that I set forth in my opening report.

D. There are no objective indicia of nonobviousness.

213. Throughout his rebuttal report, Dr. Toth incorporates by reference the opinions in his opening report on alleged objective evidence that he contends shows that the asserted claims would not have been obvious. (*E.g.*, Toth Rebuttal Rept. ¶¶ 367, 588, 651.) I addressed Dr. Toth's opinions on objective indicia in my rebuttal report, which I incorporate by reference here. For the same reasons discussed in my rebuttal report, it remains my opinion that there is no relevant evidence of objective indicia of nonobviousness for the asserted claims, and that there is clear and convincing evidence that each asserted claim would have been obvious to a POSA as of March 2008. (Heinecke Rebuttal Rept. ¶¶ 58-196.)

VII. CONCLUSION

214. In sum, for the reasons discussed above, as well as the reasons discussed in my opening report and my rebuttal report, it is my opinion that each of the asserted claims would have been obvious to a POSA as of March 2008 in view of the prior art.

I hereby declare that all of the statements made herein are true of my own knowledge and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Date: June 7, 2019

Jay W. Heinecke, M.D.